SUPPLEMENTARY INFORMATION

Childhood "bronchitis" and respiratory outcomes in middle-age: a prospective cohort study from age 7 to 53 years

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Methods E1. Data collection and additional clinical definitions

E1a. Spirometry testing

Pre- and post-BD spirometry was performed using the EasyOneTM ultrasonic Spirometer (ndd, Medizintechnik, AG, Switzerland). Participants were asked not to smoke for 4-6 hours prior to testing. Each subject was required to perform at least three pre- and three post-BD trials that met American Thoracic Society (ATS) and European Respiratory Society (ERS) acceptability and repeatability criteria [1]. The highest value for FEV_1 and FVC from acceptable and repeatable trials was recorded. Spirometry was repeated ten minutes after the administration of 300µg of salbutamol via spacer.

E1b. Additional clinical definitions

Exposure at age 7

Childhood bronchitis was defined by an affirmative response by parents/guardian to the 1968 survey question: "Has he/she at any time in his/her life suffered from attacks of bronchitis or attacked of cough with sputum (phlegm) in the chest ("loose" or "rattly" cough)?". **Childhood bronchitis frequency** was defined by responses to the question: "Since the attacks began, approximately how many has he/she had altogether?", with the following options: one attack only; 2-5 attacks; 6-10 attacks; 11-20 attacks; and over 20 attacks. **Childhood bronchitis duration** was defined by: "On average (as near as you can say), how long do these attacks usually last (with usual treatment)?", with the following options: less than 12 hours; a day; a week; a month; "continuous" (never from of loose cough for more than a day or two). The four mutually exclusive groups were defined using these two stem questions (see 4-level definition in the main text). A cut-off of >5 episodes of at least one month duration was used because there were two few participants to conduct the analysis with a single episode as an intermediate category.

Only for the mediation analyses, childhood bronchitis as the exposure was expressed as a binary variable, defined by five or more episodes of any duration by age seven.

Other outcomes at age 53

Chronic bronchitis-ever was defined by affirmative responses, "Have you, at any time in your life, suffered from with phlegm (sputum) in the chest (with or without a cold)?" and "Have you had this cough with phlegm on most days for at least three months and for two years in a row?" at age 53.

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Doctor-diagnosed asthma-ever was defined by the self-report of "ever having asthma" that was "confirmed by a doctor" at age 53. ***Doctor-diagnosed ever-asthma after 7 years*** was the age of asthma onset recalled by the participant during middle-age (either at mean age of 43 or 53 years)

Doctor-diagnosed pneumonia-ever was defined by the self-report of "ever having pneumonia" that was "confirmed by a doctor" at age 53. Doctor-diagnosed ever-pneumonia occurring 'before age 7' and 'at or after age 7' was recalled by the participant during middle-age (at mean age 53).

Confounders at age 7

The occupation of the participants' fathers when they were seven-years old was used as a proxy for ***socioeconomic class (1968)***, coded in accordance with the Australian Standard Classification of Occupations (ASCO) four-digit codes [2]. For paternal occupation, these codes were then grouped into five major skill groups: i) Managers/ professionals; ii) Associate professionals; iii) Tradespersons and advanced clerical; iv) Intermediate clerical and production; v) Elementary clerical, labourers, and related workers.

Rurality was assigned to the school attended by the participant at the time of the original 1968 survey. Categories included "inner regional Australia", "outer regional Australia", "remote Australia", and "very remote Australia" [3]. These categories were derived directly from pre-specified options of the questionnaire.

Maternal and paternal smoking were defined by an affirmative response of the respective parent or guardian to the 1968 survey question "Do you smoke every day (or six days out of seven)"; and if yes, then "How much do you smoke?" followed by three options: "more than 20 cigarettes a day; six to 20 cigarettes a day; less than 6 cigarettes a day". These categories were derived directly from pre-specified options of the questionnaire.

Parental history of bronchitic symptoms was defined by answers to the 1968 survey questions of mothers and fathers (or guardians) separately which included: 1) Do you suffer from chronic bronchitis, or from more than one attack of bronchitis every three years or so? Or, 2) Do you usually have a cough either first thing in the morning or some time during the day? Or, 3) Do you usually clear or bring up some phlegm (sputum) from your chest in the morning or some time during the day, where "usually" means on three or four days in the week, or for three or four months of the year. A positive family history was defined by at least one parent who self-reported at least one of cough, sputum, or bronchitis at the same time as reporting bronchitic episodes for their child who participated in the TAHS study.

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Effect modifiers (in addition to sex-differences)

Childhood asthma/wheezing was defined by the presence of asthma and/or wheezy breathing within the preceding 12 months in response to the 1968 survey question, "Has he/she at any time in his/her life suffered from attacks of asthma or of wheezy breathing?"

Ever-smoking was defined by self-reporting the equivalent of smoking 100 cigarettes during their lifetime. A distinction between current and past smoking was not relevant to the interaction analysis

Methods E2. Additional statistical methods

E2a. Derivation of lung function variables

Raw lung function values (measured in mL or as a ratio) were converted into z-scores using established reference values [4], with lung function expressed as difference from the expected mean, in standard deviation units, based on the individuals age, sex, height and ethnicity. The z-score values for each participant were then used as the outcome in linear regression models. As such, the coefficients represent the associations between exposures and lung function values expressed as z-scores (standard deviation units); i.e. the coefficient represents the change in z-score for each continuous lung function outcome for the exposed category compared with the reference category.

E2b. Selection of confounder variables

Regression models were adjusted for potential confounders of the bronchitis-respiratory outcome relationship including paternal occupational class [2], parental history of bronchitic episodes and symptoms that was prospectively-collected, rurality of primary school, sibling number and sex for the non-lung function analyses. These were informed via a directed acyclic graph drawn in Daggity http://www.dagitty.net/ [5] (see figure below).

Parental smoking at age seven was included in models, although its true temporality with childhood bronchitis could not be confirmed. Linearity when the sibling number variable was expressed as quintiles was confirmed using the fp command in Stata (data not shown).

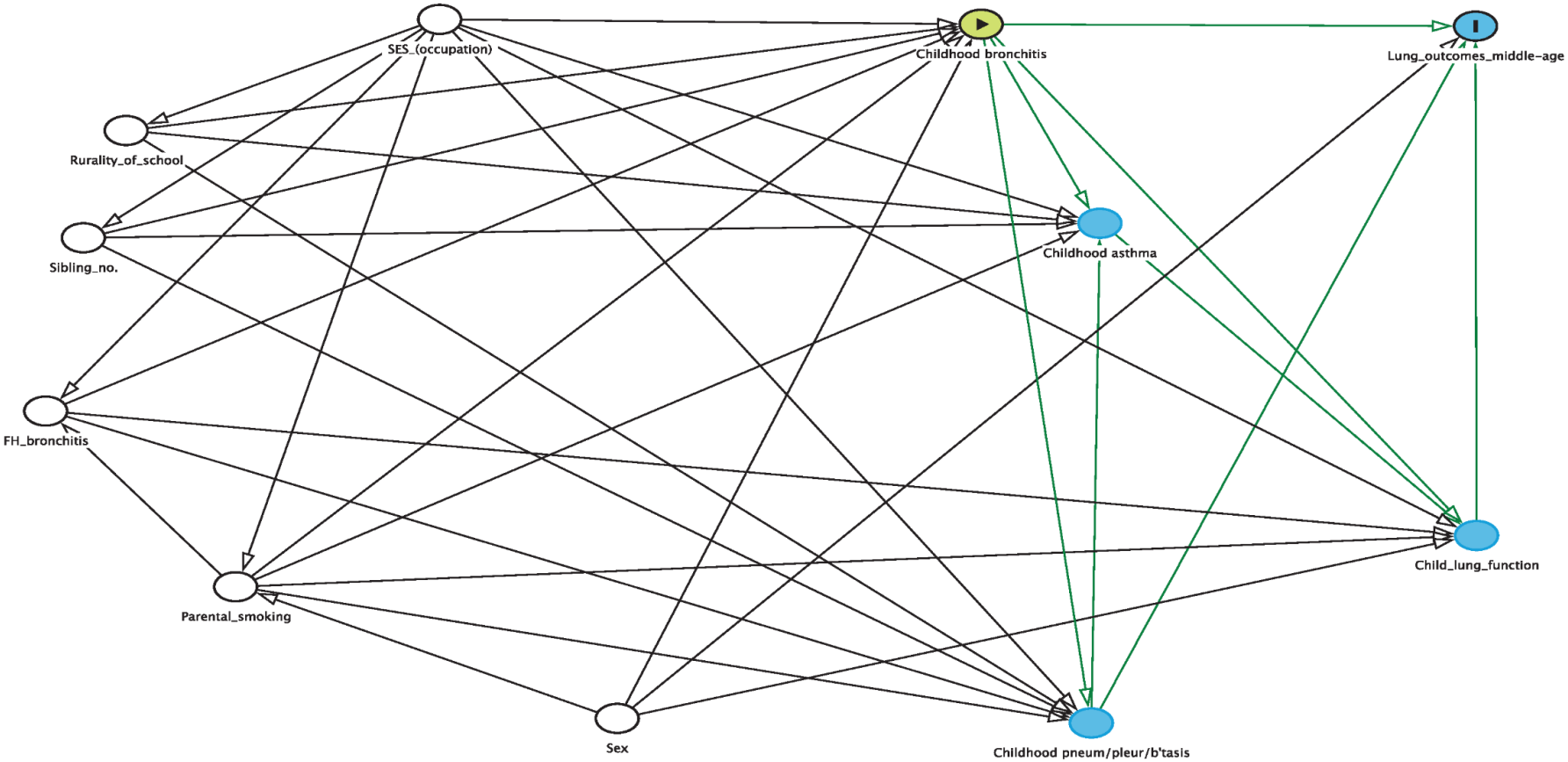

Figure: Directed acyclic graph

E2c. Mediation analyses

Childhood asthma, pneumonia-pleurisy FEV_1 at seven years were considered as potential confounders for corresponding adult outcomes, however, these factors were confirmed to be intermediaries and/or mediators of the relationship via causal mediation analysis using the medeff command in Stata [6, 7]. Therefore, the analyses of asthma and lung function outcomes were stratified by childhood asthma/wheezy breathing.

Table E1. Mediation of the childhood bronchitis-adult lung outcome relationships by the corresponding pneumonia/asthma/lung function feature at age 7

Lung outcome in middle-age	**Mediation analysis effect [% (95%CI)] †‡**			**% of total effect mediated §**
	Indirect effect	**Direct effect**	**Total effect**	
Dr-diagnosed pneumonia-ever	+2.45 (1.3-4.7)	+4.98 (1.5-8.8)	+7.87 (3.0-13.2)	31.1%
Dr-diagnosed asthma-ever	+13.25 (9.4-16.8)	+8.32 (4.4-12.5)	+21.80 (15-28)	60.8%
Current asthma	+4.95 (2.6-8.1)	+2.22 (-0.4, 5.3)	+8.01 (2.8-14.7)	61.8%
Pre-BD FEV_1	–3.13 (-7.3, +0.6)	–5.30 (-29, +17)	–8.43 (-36, +18)	37.1%
Pre-BD FVC	+2.16 (-1.8, +6.1)	–6.47 (-25, +11)	–4.31 (-27, +17)	n/a
Pre-BD FEV_1/FVC	–7.40 (-11, -4.3)	+2.28 (-7.6, +11)	–5.12 (-18, +7.4)	n/a
Post-BD FEV_1	–3.38 (-7.3, +0.3)	–2.19 (-13, +7.7)	–5.57 (-20, +8.0)	60.7%
Post-BD FVC	+1.92 (-2.2, +5.8)	–3.02 (-12, +5.3)	–1.09 (-14, +11)	n/a
Post-BD FEV_1/FVC	–7.81 (-11, -4.6)	–0.45 (-10, +8.6)	–8.26 (-21, +4.1)	94.6%

Definitions of Abbreviations: BD, bronchodilator; FEV_1,forced expiratory volume in one second; FVC, forced vital capacity

† Of the two 'average causal mediation effects', the lowest indirect effect estimate was used

‡ Adjusted for sex, paternal occupation, family history bronchitis, rurality of school, parental smoking, sibling number, and childhood asthma for the adult asthma outcomes

§ % mediated of total effect was not estimated for analyses in which there were opposing direct and indirect effects

Main findings from the mediation analyses:

- childhood asthma/wheezing was a partial mediator of the child bronchitis and adult asthma outcomes
- childhood pneumonia/pleurisy was a partial mediator of the child bronchitis and adult pneumonia outcome

- childhood FEV_1 was a stronger mediator of the child bronchitis and adult spirometry outcomes

Causal Mediation Analysis [6, 7] was used to determine the extent to which the total 'effect' of childhood bronchitis taken as a binary variable (≤5 and >5 episodes) on selected lung function outcomes was mediated by their corresponding childhood feature. Specifically, this relates to the relationship between childhood bronchitis and adult pneumonia-ever (mediated by childhood pneumonia-pleurisy); adult asthma (mediated by childhood asthma); and continuous adult lung function (mediated by childhood lung function, pre-bronchodilator). This analysis partitions the **total effect** into an **indirect effect** of childhood bronchitis on adult lung outcomes (childhood bronchitis acting through the mediator and then the mediator acting on the adult lung outcome) and a **direct effect** of childhood bronchitis on adult lung outcomes (that does not act through changes in the mediator induced by childhood bronchitis).

Notably, there was substantial mediation of relationships between childhood bronchitis and adverse lung outcomes in middle-age. For adult doctor-diagnosed pneumonia recalled in middle-age, the percent of the total effect mediated by childhood pneumonia/pleurisy was 31.1%. For adult doctor-diagnosed asthma, this was mediated by childhood asthma/wheezing by approx. 61%. Mediation for continuous lung function outcomes by childhood spirometry were variable, but the percent of total effect mediated for post-BD FEV_1/FVC levels was estimated to be as high as 94.6%.

Results E1. Missing data

Table E2a. Missing data from childhood in the entire TAHS cohort

Clinical feature in childhood N=8,583	**Lung conditions reported at age 53 [n(%)]**			**Lung function measured at age 53 [n(%)]**		
	Complete cases (n=3202)	**Missing data (n=5381)**	**p-value †**	**Complete cases (n=2379)**	**Missing data (n=6204)**	**p-value †**
Childhood bronchitis	-	-	0.011	-	-	0.041
None	1680 (52)	2850 (55)	-	1238 (52)	3292 (55)	-
Non-recurrent (1-5 episodes, any duration)	902 (28)	1429 (28)	-	686 (29)	1645 (28)	-
Recurrent (≥5 episodes), non-protracted	598 (18)	800 (16)	-	427 (18)	951 (16)	-
Recurrent, protracted	**42 (1.3)**	**59 (1.2)**	**-**	**28 (1.2)**	**73 (1.2)**	**-**
Age [years (SD)]	6.50 (0.3)	6.51 (0.3)	0.315	6.50 (0.3)	6.51 (0.3)	0.162
Sex [% male]	1576 (49)	2817 (52)	0.005	1156 (49)	3237 (52)	0.003
Rurality of School [n(%)]	-	-	0.225			0.124
Inner city	1868 (58)	3137 (60)	-	1397 (59)	3608 (59)	-
Outer regional	1238 (39)	1934 (37)	-	919 (39)	2253 (37)	-
Remote	96 (3.0)	173 (3.3)	-	63 (2.7)	206 (3.4)	-
Paternal occupation [n(%)]	-	-	<0.001			<0.001
Managers/ professionals (highest)	795 (25)	875 (18)	-	584 (25)	1086 (19)	-
Elementary clerical/ labour/ other (lowest)	379 (12)	779 (16)	-	258 (11)	900 (16)	-
Familial bronchitis [n(%)]	-	-	<0.001	-	-	0.001
One parent	1026 (32)	1650 (36)	-	775 (32)	1921 (35)	-
Both parents	122 (3.8)	215 (4.7)	-	90 (3.8)	247 (4.5)	-
Mother's smoking [n(%)]	1080 (34)	1953 (40)	<0.001	772 (32)	2261 (40)	<0.001
Father's smoking [n(%)]	1879 (59)	3006 (65)	<0.001	1381 (58)	3504 (64)	<0.001
Sibling number [mean (SD)]	2.6 (1.6)	2.4 (1.9)	<0.001	2.5 (1.6)	2.4 (1.9)	<0.001
Spirometry at age 7 (z-score)	-	-	-	-	-	-
zFEV$_1$ [mean (SD)]	-	-	-	–0.06 (0.9)	–0.08 (1.0)	0.390
zFVC [mean (SD)]	-	-	-	–0.16 (0.9)	–0.18 (0.9)	0.565
zFEV$_1$/FVC [mean (SD)]	-	-	-	+0.19 (0.9)	+0.20 (1.0)	0.625

Definition of abbreviations: IQR, interquartile range, SD, standard deviation

† Chi-squared and nptrend tests were used to derive p-values

For the present analysis, 45.1% (n=3,202) of the 7,099 participants of the original cohort who had complete childhood bronchitis data also had complete outcome and confounder data. While there was some variation in the prevalence of childhood bronchitis subgroups by missing data categories, there was little difference between the percentages missing for the main exposure subgroup of "recurrent-protracted" childhood bronchitis (1.2-1.3%).

Missing data of the confounding variables included 1.6% for rurality; 6.9% for occupation; 6.4% mother's smoking; 8.6% father's smoking and 8.8% familial bronchitis, and this was somewhat greater for male participants of lower socio-economic status with a familial history of bronchitis and parental smoking. However, for the recurrent-protracted childhood bronchitis group, this missing confounder data reduced the number of cases from 44 to 42 only.

Table E2b. Missing data and an earlier follow-up in middle-age (with some selection)

Clinical feature at mean age 43 years (10 years prior to outcomes at age 53) N=5,723	**Lung conditions reported at age 53 [n(%)]**			**Lung function measured at age 53 [n(%)]**		
	Complete cases (n=2957)	**Missing data (n=2766)**	**p-value †**	**Complete cases (n=2215)**	**Missing data (n=3508)**	**p-value †**
Doctor-diagnosed asthma-ever [n(%)]	654 (22)	591 (21)	0.492	492 (22)	753 (21)	0.505
Self-reported chronic bronchitis [n(%)]	165 (5.6)	185 (6.8)	0.079	122 (5.6)	228 (6.6)	0.130
† Chi-squared tests were used to derive p-values						

The differences in corresponding outcomes of doctor-diagnosed asthma-ever at an earlier time-point in middle-age as a proxy for the outcome at mean age 53 years, approx. 10 years later was not significant, and did not reach the $p<0.05$ threshold for self-reported chronic bronchitis.

Overall, substantial collider bias seems unlikely as participation was minimally associated with the exposure, or proxies of the outcome.

Results E2. Effect modification by childhood asthma/wheezing

Table E3: *Interactions between the effects of childhood bronchitis on lung conditions in middle-age, by childhood asthma-wheezing status*

Lung condition at age 53	Cases (n)	Childhood bronchitis severity at age 7 [OR (95% CI), N=3,202] †‡§						
		No childhood asthma (n=2,652)			Childhood asthma (n=550)			
		Non-recurrent (n=735)	Recurrent bronchitis (n=310)	Recurrent and protracted (n=17)	Non-recurrent (n=166)	Recurrent bronchitis (n=269)	Recurrent and protracted (n=25)	p-int value
CB-current	158	0.85 (0.55–1.32)	0.79 (0.43–1.46)	§	0.60 (0.20–1.79)	0.87 (0.34–2.26)	§	0.885
CB-ever	275	0.84 (0.60–1.18)	0.86 (0.54–1.37)	§	0.98 (0.42–2.31)	1.17 (0.54–2.57)	§	0.445
Asthma-current	395	1.34 (1.00–1.82) ^	0.99 (0.63, 1.57)	4.29 (1.45–12.6) **	0.98 (0.53–1.83)	1.66 (0.95, 2.91)	1.67 (0.63–4.41)	0.063
Asthma-ever	804	1.19 (0.98–1.44)	1.25 (0.96–1.63)	2.58 (1.07–6.21) *	0.69 (0.43–1.10)	1.49 (0.95–2.33)	4.63 (1.31–16.3) *	0.005
From ≥ 7 years	783	1.21 (0.99–1.47) ^	1.26 (0.96–1.65)	2.67 (1.11–6.43) *	0.73 (0.44–1.20)	1.47 (0.91–2.38)	5.70 (1.60–20.3) **	0.012
Pneumonia-ever	574	1.42 (1.12–1.81) **	1.71 (1.25–2.34) **	4.01 (1.49–10.8) **	1.10 (0.58–2.01)	1.63 (0.91–2.93)	1.81 (0.66–4.97)	0.552
From ≥ 7 years	460	1.30 (1.00–1.68) ^	1.67 (1.19–2.33) **	1.96 (0.53–7.25)	1.05 (0.51–2.15)	1.41 (0.73–2.72)	1.69 (0.55–5.17)	0.341

Definitions of abbreviations: BD, bronchodilator; CB, chronic bronchitis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T_Lco, carbon monoxide transfer factor of the lung

*^p<0.06 *p<0.05 **p<0.01 ***p<0.001*

†Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of "loose, or rattly" or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)

‡ Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex

§ Cells that had <5 cases and negative findings

Table E4: Interactions between the effects of childhood bronchitis on lung function in middle-age, by childhood asthma-wheezing status

		Childhood bronchitis severity at age 7 [OR (95% CI), N=2,379] †‡						
Lung function at age 53 §	**Model (N)**	**No childhood asthma (n=1,983)**			**Childhood asthma (n=396)**			
		Non-recurrent (n=559)	**Recurrent bronchitis (n=233)**	**Recurrent and protracted (n=14)**	**Non-recurrent (n=126)**	**Recurrent bronchitis (n=194)**	**Recurrent and protracted (n=14)**	**p-int value**
Pre-BD $zFEV_1$	2379	–0.11 (–0.28, +0.07)	–0.01 (–0.26, +0.23)	‖	+0.46 (–0.59, +1.51)	–0.19 (–1.18, +0.79)	‖	0.063
Post-BD $zFEV_1$	2354	–0.07 (–0.17, +0.03)	–0.03 (–0.17, +0.11)	‖	–0.21 (–0.56, +0.14)	–0.35 (–0.67, –0.02)*	‖	0.190
BDR ΔFEV_1 (ml)	2344	–2.54 (–15.9, +10.8)	–10.48 (–29.1, +8.19)	‖	–57.05 (–101.8, –12.3)*	–37.18 (–78.7, +4.35)	‖	0.075
Pre-BD zFVC	2378	–0.07 (–0.20, +0.07)	–0.03 (–0.22, +0.16)	‖	+0.07 (–0.77, +0.90)	–0.33 (–1.12, +0.45)	‖	0.199
Post-BD zFVC	2354	–0.05 (–0.14, +0.04)	–0.05 (–0.17, +0.08)	‖	–0.42 (–0.72, –0.12)**	–0.37 (–0.65, –0.09)**	‖	0.057
BDR ΔFVC (ml)	2343	–2.85 (–17.7, +12.0)	–9.39 (–30.2, +11.4)	‖	–29.4 (–81.2, +22.4)	+6.71 (–41.4, +54.8)	‖	0.242
Pre-BD $zFEV_1$/FVC	2378	–0.06 (–0.15, +0.03)	+0.03 (–0.10, +0.16)	‖	+0.43 (+0.11, +0.74)**	+0.16 (–0.13, +0.46)	‖	0.011
Pre-BD airflow obstruction □	2378	1.28 (0.86–1.90)	1.19 (0.69–2.07)	‖	0.34 (0.14–0.87)*	0.71 (0.33–1.53)	‖	0.035

Post-BD $zFEV_1/FVC$	2354	–0.05 (–0.14, +0.04)	+0.01 (–0.11, +0.14)	‖	+0.33 (+0.01, +0.66)*	+0.01 (–0.29, +0.31)	‖	0.033
Post-BD airflow obstruction □	2342	1.24 (0.74–2.08)	1.00 (0.47–2.12)	‖	0.45 (0.12–1.69)	0.85 (0.28–2.60)	‖	0.370
Spirometric restriction □	2239	1.61 (0.82–3.17)	1.53 (0.56–4.18)	‖	‖	‖	‖	0.150
zT_Lco	2285	+0.03 (–0.07, +0.13)	+0.02 (–0.12, +0.16)	‖	–0.13 (–0.44, +0.19)	–0.03 (–0.32, +0.26)	‖	0.500
zKCO	2285	+0.05 (–0.06, +0.15)	+0.11 (–0.03, +0.26)	‖	+0.10 (–0.21, +0.42)	+0.30 (0.000, +0.59) ^	‖	0.655
zVA	2285	–0.02 (–0.11, +0.08)	–0.11 (–0.25, +0.02)	‖	–0.30 (–0.63, +0.04)	–0.40 (–0.71, –0.09) *	‖	0.158

Definitions of abbreviations: BD, bronchodilator; BDR, bronchodilator response; CB, chronic bronchitis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T_Lco, transfer factor of the lung for carbon monoxide; $zFEV_1/FVC<LLN$, airflow obstruction

*^p=0.050 *p<0.05 **p<0.01 ***p<0.001*

†Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of "loose, or rattly" or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)

‡ Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex

§ Lung function measured in z-scores which, by definition, has a mean of 0 and standard deviation of 1

□ Case numbers: pre-BD airflow obstruction ($zFEV_1/FVC<LLN$), n= 191; post-BD airflow obstruction, n = 108; spirometric restriction (post-BD $zFVC<LLN$ and $zFEV_1/FVC \geq LLN$), n = 56

‖ Too few cases or residual degrees of freedom to derive point estimates; for Post-BD zFVC<LLN, failure was predicted perfectly for those with childhood asthma/wheezing

For participants with a history of childhood asthma/wheezing only, compared with the reference group of no childhood bronchitis, those with fewer than five episodes of childhood bronchitis of any duration had borderline lung function deficits consistent with a non-obstructed pattern (p-interaction <0.1). A change in lung function was regarded to be significant if the difference was >100 mL and >0.5 SD, so the associations did not quite reach clinical significance and included: reduced post-BD FVC [z-score –0.42 SD (95%CI: –0.72, –0.12), p=0.006], increased pre-BD FEV_1/FVC [+0.43 (+0.11, +0.74), p=0.008] and post-

BD FEV_1/FVC [+0.33 (+0.01, +0.66), p=0.043] despite an increased pre-BD FEV_1, as well as an associated 3-fold decrease in the odds for pre-BD airflow obstruction [OR 0.34 (+0.14, +0.87), p=0.024].

Results E3. Sex-differences

Table E5: *Interactions between the effects of childhood bronchitis on lung conditions in middle-age, by sex*

		Childhood bronchitis severity at age 7 [OR (95% CI), N=3,202] †‡						
Lung condition at age 53	**Cases (n)**	**Females with childhood bronchitis (n=1,626)**			**Males with childhood bronchitis (n=1,576)**			
		Non-recurrent (n=470)	**Recurrent, non-protracted (n=252)**	**Recurrent-protracted (n=19)**	**Non-recurrent (n=432)**	**Recurrent, non-protracted (n=327)**	**Recurrent-protracted (n=23)**	**p-int value**
CB-current	158	0.59 (0.31–1.11)	0.67 (0.31–1.44)	§	1.13 (0.67–1.90)	1.15 (0.66–2.02)	§	0.300
CB-ever	275	0.80 (0.51–1.23)	0.94 (0.55–1.59)	§	1.05 (0.68–1.61)	1.19 (0.76–1.87)	§	0.518
Asthma-current	395	1.29 (0.91–1.84)	1.93 (1.30, 2.88) **	5.88 (2.26–15.3) ***	1.77 (1.20–2.62) **	3.07 (2.07, 4.53) ***	3.87 (1.44–10.4) **	0.323
Asthma-ever	804	1.24 (0.99–1.56) ^	2.28 (1.74–2.99) ***	6.10 (2.36–15.8) ***	1.46 (1.13–1.88) **	3.29 (2.53–4.28) ***	7.64 (3.26–17.9) ***	0.278
Pneumonia-ever	574	1.67 (1.25–2.22) **	2.06 (1.46–2.91) ***	6.12 (2.41–15.6) ***	1.14 (0.81–1.60)	1.95 (1.38–2.75) ***	1.52 (0.54–4.26)	0.097

	Aged ≥ 7 years	460	1.61 (1.17–2.20) **	1.89 (1.30–2.75) **	3.49 (1.13–10.8) *	0.94 (0.64–1.38)	1.67 (1.15–2.44) **	§	0.114
	Aged < 7 years	114	1.96 (1.05–3.65) *	2.05 (1.52–6.09) **	22.5 (6.60–76.4) ***	2.62 (1.24–5.58) *	4.01 (1.87–8.61) ***	§	

Definitions of abbreviations: BD, bronchodilator; CB, chronic bronchitis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T_Lco, carbon monoxide transfer factor of the lung

*^p<0.06 *p<0.05 **p<0.01 ***p<0.001*

†Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of "loose, or rattly" or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)

‡ Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex

§ Cells that had <5 cases and negative findings

Stratification of the analyses relating to lung conditions as outcomes were limited by few case numbers but found some association between childhood bronchitis and recalled doctor-diagnosed pneumonia-ever for females (p-interaction between 0.097-0.114).

Notably, chronic airway infection such as bronchiectasis unrelated to cystic fibrosis has some predominance in non-smoking females [8, 9], although it is possible that females could report pneumonia-like symptoms more frequently than males, similarly to the increase in dyspnoea reported by females with chronic obstructive pulmonary disease [10]. This potential increase in pneumonia prevalence contrasts the observed increase in severity of community-acquired pneumonia and its related mortality in older males [11, 12].

Results E4. Potential effect modification by ever-smoking

Table E6: *Interactions between the effects of childhood bronchitis on lung conditions in middle-age, by smoking-ever status*

		Childhood bronchitis severity at age 7 [OR (95% CI), N=3,176] †‡						
Lung condition at age 53	**Cases (n)**	**Non-smokers at age 53 with childhood bronchitis (n=1,316)**			**Ever-smokers by age 53 with childhood bronchitis (n=1,860)**			
		Non-recurrent (n=377)	**Recurrent, non-protracted (n=251)**	**Recurrent-protracted (n=20)**	**Non-recurrent (n=514)**	**Recurrent, non-protracted (n=321)**	**Recurrent-protracted (n=22)**	**p-int value**
CB-current	158	1.16 (0.53–2.51)	1.07 (0.42–2.74)	5.40 (1.30–22.5) * (n=3 cases)	0.76 (0.48–1.22)	1.00 (0.60–1.66)	§	0.389
CB-ever	275	1.21 (0.71–2.05)	1.08 (0.57–2.03)	§	0.79 (0.54–1.15)	1.15 (0.77–1.73)	§	0.425
Asthma-current	395	1.19 (0.78–1.85)	2.30 (1.50, 3.56) ***	3.04 (1.03–8.94) *	1.70 (1.22–2.37) **	2.54 (1.76, 3.65) ***	6.13 (2.51–15.0) ***	0.456
Asthma-ever	804	1.32 (0.97–1.81)	3.07 (2.21–4.28) ***	7.63 (2.93–19.9) ***	1.39 (1.08–1.81) *	2.87 (2.15–3.82) ***	8.33 (3.32–21.0) ***	0.905
Pneumonia-ever	574	1.63 (1.13–2.34) **	2.42 (1.64–3.58) ***	5.13 (1.98–13.3) **	1.32 (1.00–1.75) ^	1.83 (1.33–2.51) ***	2.28 (0.90–5.73)	0.509

Definitions of abbreviations: BD, bronchodilator; CB, chronic bronchitis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OR, odds ratio; T_Lco, carbon monoxide transfer factor of the lung

*^p=0.051 *p<0.05 **p<0.01 ***p<0.001*

†Parent-reported bronchitis by age 7 categorized into none (reference = 1, not shown), non-recurrent, recurrent (>5 episodes of "loose, or rattly" or chesty cough lasting <1 month on average), and recurrent-protracted (>5 episodes, ≥1 month average duration)

‡ Multivariable models were adjusted for rurality of school, paternal occupation, family history of bronchitis, sibling number, maternal and paternal smoking, and participant sex

§ Cells that had <5 cases and negative findings

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